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EXAMINER	
BALLARD, KIMBERLY	

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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/441,140	SOLOMON, BEKA	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *177 and 210-228* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *177 and 210-228* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. Claims 210-214 have been amended and new claims 215-228 have been added as requested in the amendment filed on September 23, 2009. Following the amendment, claims 177 and 210-228 are pending in the instant application.

Claims **177** and **210-228** are under examination in the instant office action.

Reissue Applications

2. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,688,651 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

Withdrawn Objections and Claim Rejections

3. The rejection of claims 212 and 213 under 35 U.S.C. 103(a) as being unpatentable over Majocha et al. US Patent No. 5,231,000, as evidenced by Solomon

(*Expert Opin Biol Ther.* 2002, 2(8): 907-917), and in view of Boerner et al. WO 91/17769, is withdrawn in view of Applicant's amendments to the claims.

4. The rejection of claims 177 and 210-214 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. EP 0613007 A2, in view of Cordell (*Annu. Rev. Pharmacol. Toxicol.* Jan 1994, 34: 69-89), and Spillantini et al. (*Proc. Natl. Acad. Sci. USA*, May 1990, 87: 3947-3951), as evidenced by Kirschner et al. (*Proc. Natl. Acad. Sci. USA*, Oct 1987, 84: 6953-6957), is withdrawn in view of Applicant's amendments to the claims.

Maintained and New Claim Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 177 and 210-228 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for reasons of record and is further applied to new claims 215-228.

7. In the response filed September 23, 2009, Applicant argues that according to Example 13 of the Written Description Training Materials from the PTO website, the present claims are supported by the instant specification because there is at least one example of the claimed antibody present, which is more than the specification of the guideline's Example 13 has. Applicant asserts that the present claims differ from the claim of Example 13 in that they are narrower than the recitation of antibodies in Example 13. Applicant contends that the present claims do not cover every antibody that is specific to an epitope within 1-28 of Aβ, but requires another screen of the selected antibodies to select only those that inhibit Aβ aggregation or cause disaggregation of Aβ aggregates. In view of the disclosure of the antigen to which the antibody is specific, the screening assays for determination of the claimed properties, and the well known structure-function relationship of antibody to antigen, Applicant argues that one of skill in the art would understand that the inventor was in possession of the claimed genus of antibodies. Further, with respect to the breadth of the term "genetically engineered antibody", Applicant contends that once one of ordinary skill in the well-developed and mature antibody art is in possession of a monoclonal antibody with certain properties, it is a routine matter to genetically engineer it to obtain a single-chain, humanized, etc. antibody that maintains the binding characteristics of the starting material.

8. Applicant's arguments have been fully considered but they are not persuasive. Claims 177 and 210-218, as amended, are now drawn to compositions and methods of making such compositions comprising a genus of genetically-engineering antibody

molecules, including both antibodies and fragments thereof, having a specific functional property, and for which applicant has only disclosed a single species within the genus. For example, the recitation of an antibody capable of inhibiting aggregation of soluble β-amyloid in a subject "to an extent at least as great as that obtainable with antibody AMY-33" does not meet the written description provision of 35 U.S.C. 112, first paragraph, because there is insufficient guidance and direction of the genus of antibodies broadly encompassed by the claimed invention.

Moreover, contrary to applicant's assertions that the presently claimed invention is consistent with the claims of Example 13 of the PTO's Written Description Guidelines, it is noted that instant claims 177, 210-214 and 219-224, as amended, do not recite any actual binding specificity for the claimed antibody or fragments thereof. The claims merely recite functional properties for the antibody molecules, or that the antibody "is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen". However, this product-by-process limitation does not serve to limit the antibody's structure or even define its binding epitope, because as broadly interpreted, the immunogen is not limited to the peptide (only the peptide is limited to what it may consist of) and thus other immunogens may be present addition to a peptide consisting Aβ 1-28. Therefore, there is no antigen-binding specificity of the claimed antibody or fragments thereof. The specification does not identify a structure/function correlation for antibodies capable of inhibiting β-amyloid aggregation, nor is there identification of any particular portion of the structure that must be conserved. Distinguishing structural

characteristics that could help to identify members of the claimed genus of antibodies are lacking from the instant specification.

Regarding antigen specificity, the art recognizes that antibodies are immunoglobulin molecules that are formed in response to a particular antigen, and possess the ability to react *in vitro* and *in vivo* specifically and selectively with the antigenic determinants or epitopes eliciting their production or with an antigenic determinant closely related to the homologous antigen. It has been well established in the art that the antigen binding specificity is critical to how the skilled artisan would employ antibodies in various modalities (e.g., affinity purification, detection or diagnostic assays, bioassays, treatment), including those consistent with the instant disclosure (such as therapeutic applications). In particular, the instant specification discloses that the AMY33 antibody of the present invention, for example, has binding specificity for β-amyloid but the instant claims do not recite such antigen specificity.

Further, all of the claims recite a repertoire of fragments of genetically-engineered antibody molecules, but no structural features of such fragments or antigen-binding specificity is recited for the claimed fragments. Thus, the claim language reads on small, ill-defined peptides or amino acid sequences, which may not even comprise the antigen-binding region of the claimed antibody. And because the structure of the claimed antibody also is not defined, particularly for genetically-engineered antibodies which may have any number of structural changes applied to the parent monoclonal antibody from which they were derived, the claims broadly encompass any peptide sequence capable of inhibiting β-amyloid aggregation and/or disaggregated β-amyloid

aggregates. Such a genus of peptide molecules is clearly not supported by the specification as filed.

With respect to claims 177 and 210-218, the claims broadly recite a therapeutic composition comprising a genetically-engineered antibody, or fragment thereof, that inhibits aggregation of β-amyloid or maintains the solubility of soluble beta-amyloid *to an extent at least as great as that obtainable with antibody AMY-33* (emphasis added), and is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen. Such would imply the use and possession not only of antibodies having anti-aggregating abilities the same as that of the mAb AMY-33, but also of antibodies having anti-aggregating properties exceeding that of AMY-33. Therefore, the claims are drawn to a genus of genetically-engineered antibodies having a degree of functional activity equal to or greater than the functional activity of AMY33.

MPEP § 2163(a)(ii) states:

> The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus **only if** the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)
>
> The Federal Circuit has explained that a specification cannot always support expansive claim language and satisfy the requirements of 35 U.S.C. 112 "merely by clearly describing one embodiment of the thing claimed." *LizardTech v. Earth Resource Mapping*, Inc., 424 F.3d 1336, 1346, 76 USPQ2d 1731, 1733 (Fed. Cir.

> 2005). The issue is whether a person skilled in the art would understand applicant to have invented, and been in possession of, the invention as broadly claimed.
>
> What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*.

The instant specification does not provide support or guidance for classifying antibodies based upon a particular level of functional activity, and certainly does not provide guidance or support for a class of antibodies determined to meet or exceed the functional ability of the antibody AMY-33 to inhibit β-amyloid aggregation. Such genetically-engineered antibodies and fragments thereof having a specific degree of activity thus represent a genus of antibody molecules for which Applicant has only demonstrated one species within the genus, wherein the single embodiment of AMY33 does not constitute a "representative number" of species such that one of skill in the art would recognize that Applicant was in possession of the invention as broadly claimed. In particular, the instant specification demonstrates that not all antibodies obtainable using residues 1-28 of β-amyloid as an immunogen or antibodies that recognize an epitope within residues 1-28 of β-amyloid possess the ability to inhibit β-amyloid aggregation. In view of this unpredictability and given the well known high level of polymorphism of immunoglobulins / antibodies, the skilled artisan would not recognize that the applicant was in possession of the vast repertoire of genetically-engineered antibody molecules encompassed by the claimed invention. Accordingly, in the

absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus nor guidance as to which of myriad of antibody molecules that are encompassed by the claimed invention would be capable of inhibiting β-amyloid aggregation to a level that meets or exceeds the ability of the single disclosed species of AMY-33 to inhibit aggregation.

As noted previously, the skilled artisan cannot envision the detailed chemical structure of the encompassed genetically-engineered antibodies, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of selection, isolation, and/or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Also as noted previously, possession may not be shown by merely describing how to obtain possession of members of the claimed genus. *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.,* 119 F.3d 1559, 1566 (Fed. Cir. 1997).

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 177 and 210-218 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The claims, as amended, recite a therapeutic composition comprising a genetically-engineered antibody that inhibits aggregation of β-amyloid or maintains the solubility of soluble beta-amyloid *to an extent at least as great as that obtainable with antibody AMY-33* (emphasis added), or a fragment of said antibody that inhibits aggregation of β-amyloid or maintains the solubility of soluble beta-amyloid *to an extent at least as great as that obtainable with antibody AMY-33*, and is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen. Such would imply the use and possession not only of antibodies have anti-aggregating abilities the same as that of the mAb AMY-33, but also of antibodies having anti-aggregating properties exceeding that of AMY-33. There is no support in the specification as originally filed for anti-β-amyloid antibodies which inhibit aggregation of β-amyloid to a particular specified degree, much less one that is described in terms of meeting or exceeding the ability of the antibody AMY-33 to inhibit β-amyloid aggregation. Such antibodies having a specific degree of activity thus represent a genus of antibodies for which Applicant has only demonstrated one species, AMY-33, within the genus. Similarly, there is no support in the specification as originally filed for a method of

making a therapeutic composition comprising an antibody comprising a method step wherein the antibody is screened for having activity at least as great as that obtainable with AMY-33. There is no *verbatim* support for the new claim language added in the last amendment, nor does it flow naturally from the disclosure as originally filed.

At pages 6-7 of the response filed September 23, 2009, Applicant asserts that the specification supports the generic idea of using an antibody that prevents aggregation as well as the specific idea of using antibody AMY-33, such as at column 6, lines 21-26 of the specification. This, Applicant remarks, provides support for the genus of an antibody which has any amount of aggregation and the species of an antibody that has the same amount of aggregation as AMY-33. In conjunction with the disclosure of "selected, highly specific monoclonal antibodies" at column 16, lines 15-21 of the specification, Applicant concludes that the concept of use of an antibody within the range of the amount of inhibition achieved by AMY-33 and above is therefore supported.

Contrary to Applicant's reasoning and as stated above, while the instant specification may generically support antibodies that inhibit protein aggregation and the specific embodiment of the anti-β-amyloid antibody AMY-33, it does not reasonably provide support for the genus of antibodies exceeding the anti-aggregating capacity of AMY-33. Moreover, in order to have such a genus of antibodies, one would have to test the anti-aggregating abilities of candidate antibodies and compare them directly to that of AMY-33. No such assay is described or implied within the specification.

Furthermore, the disclosure of a "preferred embodiment", such as the anti-β-amyloid antibody AMY-33, usually implies the highest or best embodiment achievable or known to Applicants at the time of filing. While a claimed invention is certainly not limited to preferred embodiments, which are typically the embodiments best disclosed, supported and enabled by the specification, the claimed invention must be readily supported by the specification as filed. Otherwise, this would be akin to saying that had the Wright brothers filed a patent application claiming a flying machine capable of flying at least as well as their own aircraft, this would be supportive of later claiming a genus of aircraft that included jet planes and space shuttles.

Therefore, the recitation of a single species, AMY33, does not support the recited genus of antibody molecules as currently amended and claimed.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 177, 210-213 and 215-217 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bickel et al. (*Bioconjugate Chem.* 1994, 5(2): 119-125, of record), as evidenced by Solomon (*Expert Opin Biol Ther.* 2002, 2(8): 907-917, of record), and in view of EP 0613 007 A2 to Becker et al. (published 08/31/1994; of record) and US Patent No. 4,946,778 to Ladner et al. (issued August 7, 1990). This rejection is maintained for reasons of record and is further applied to amended claims 212 and 213 and to new claims 215-217. Note that addition of the Becker reference was necessitated by Applicant's amendments to the claims.

The claims, as amended, recite a therapeutic composition comprising a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a genetically-engineered antibody or fragment thereof, wherein the antibody is obtained by genetically-engineering the DNA encoding a monoclonal antibody that inhibits aggregation of beta-amyloid or maintains the solubility of beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and is obtainable using a peptide consisting of β-amyloid 1-28 or recognizes an epitope within residues 1-28 of β-amyloid, and wherein said antibody or fragment is not conjugated with a detectable moiety. Dependent claims recite that the β-amyloid is human β-amyloid and that the genetically-engineered monoclonal antibody is a single chain antibody. However, the recitation of “a therapeutic composition” and “a pharmaceutical formulation” does not confer patentable weight because it appears in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or

the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). See also MPEP § 2111.02, section II. Accordingly, any prior art pertaining to a composition comprising the claimed antibody and a pharmaceutically acceptable carrier would meet the limitations of the claims.

Bickel et al. teach the development and characterization of a monoclonal antibody, AMY33, which was produced by immunizing animals with residues 1-28 of human β-amyloid (see p. 122, 1st paragraph under Discussion). AMY33 is taught to specifically recognize and bind to residues 1-28 of human β-amyloid (see Figure 2 on p. 122), and is demonstrated to bind to amyloid deposits in brain sections taken from AD patients (see p. 122, 1st column and Figure 3 on p. 123). In addition to suggesting that highly specific anti-β-amyloid monoclonal antibodies could be used for *in vivo* diagnostic methods that would be expected to be more specific and sensitive for Alzheimer's disease (AD) than clinical criteria (see p. 119), such as for detecting cerebral β-amyloid deposits *in vivo* in the brains of patients with AD (see Abstract), Bickel suggests the use of monoclonal antibodies for therapeutic use. For example, Bickel discusses a need for reducing the immunogenicity of such antibodies and binding proteins targeted to β-amyloid and senile plaques within the brain, such as by humanization of murine monoclonal antibodies, would facilitate their use of as neurodiagnostic or therapeutic agents in humans (see p. 124, 2nd column).

While the claimed antibody recites functional properties including inhibition of aggregation of β-amyloid and/or maintaining the solubility of soluble β-amyloid, it is noted that the AMY33 monoclonal antibody taught by Bickel et al. is the same as that described in the instant specification, and is described by the instant specification as possessing such functional characteristics. Additionally, the examiner notes that antibodies raised against the N-terminus of β-amyloid (i.e., Aβ 1-28) intrinsically have "chaperone" or anti-aggregating properties, including solubilization of existing β-amyloid aggregates and inhibition of β-amyloid aggregation, as evidenced by Solomon (see p. 909).

Thus while Bickel et al. teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a monoclonal antibody obtainable using β-amyloid 1-28 as a peptide immunogen, wherein the antibody is evidenced as being capable of inhibiting the aggregation of β-amyloid or maintaining the solubility of soluble β-amyloid by Solomon, Bickel does not teach a genetically-modified antibody that is obtained by genetically engineering the DNA encoding the monoclonal antibody, or that the genetically-engineered antibody is a single-chain antibody. Because the antibody disclosed by Bickel is AMY33, antibodies engineered from AMY33 would reasonably be expected to meet the new limitation of inhibition of β-amyloid aggregation "at least as great as that obtainable with antibody AMY-33".

Becker et al. disclose pharmaceutical formulations comprising a pharmaceutically acceptable carrier and an anti-β-amyloid antibody (see column 8, lines 19-26 and 31-42), such as for use in the diagnosis and treatment of Alzheimer's disease (column 7,

lines 39-52 and column 8, lines16-18). Monoclonal antibodies derived from various species, including mice and humans, are disclosed at column 6, lines 10-19. Thus, Becker teaches the use of anti-β-amyloid human monoclonal antibodies. Becker discloses that the greatest deterrence to the administration to humans of antibodies produced in non-human sources is the risk of hyperimmunogenicity due to the presence of constant regions from the species in which these antibodies are produced. Therefore, genetically engineering the antibodies to retain epitope specificity but reduce immunogenicity is desirable (column 6 lines 31-40). Further, Becker teaches single chain antibodies as another genetically engineered antibody for retaining the binding characteristics of the parental antibody while affording a less immunogenic format (column 7, lines 11-25). Because a single-chain antibody is a genetically-engineered antibody that is obtained by genetically engineering the DNA encoding a monoclonal antibody, as indicated in the instant claims, the limitations regarding "genetically-engineered" have been met.

Consistent with the teachings of Becker, Ladner et al. teach the production of single chain antibodies and further discloses that they may be used for essentially any use that the prior art has envisioned for monoclonal or polyclonal antibodies (column 3, lines 29-31). Ladner discloses, for example, that single chain antibodies may be used in diagnostics, therapy, *in vivo* and *in vitro* imaging, purification and biosensor applications (column 3, lines 18-24). Ladner teaches the advantages of the use of single chain antibodies to include smaller size, greater stability, reduced cost, and greater ease of genetic modifications to improve binding affinity and specificity (column

3, lines 33-48). Ladner notes that because of the smaller size, single chain antibodies may reduce immunogenicity and thus increase the safety and efficacy of therapeutic applications (column 3, lines 35-38). Ladner further teaches that the single chain antibody "can be utilized by itself, in detectably labeled form, in immobilized form, or conjugated to drugs or other appropriate therapeutic agents, in diagnostic, imaging, biosensors, purifications, and therapeutic uses and compositions. Essentially all uses envisioned for antibodies or for variable region fragments thereof can be considered for the molecules of the present invention." (emphasis added) See column 11, lines 27-34.

Upon reading the teachings of Bickel et al., the skilled artisan would have recognized the desirability of developing improved less-immunogenic compositions comprising the AMY33 antibody for the *in vivo* diagnosis or therapy of Alzheimer's disease, particularly in view of Becker's disclosure teaching the use of anti-Aβ antibodies for use in diagnostic and therapeutic applications. Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to genetically-engineer the monoclonal antibody taught by Bickel et al. to make a single-chain antibody, as taught by Becker and Ladner, with a reasonable expectation of success in producing a molecule with reduced immunogenicity, improved affinity and sensitivity, greater stability, and reduced cost of production compared to whole antibodies with a reasonable expectation of success. Similarly, it would have been obvious to make a human monoclonal anti-Aβ antibody, as taught by Becker, obtainable using a peptide consisting of residues 1-28 of Aβ because this was the immunogen used to produce the AMY33 antibody, and Bickel demonstrates that this antibody binds

specifically to brain amyloid deposits, thus evidencing the usefulness of antibodies obtained with this immunogen. Human monoclonal antibodies would also be less immunogenic when administered to humans, and thus would be advantageous for clinical applications. The motivation to produce less immunogenic antibodies was expressly provided by Bickel et al., who state at p. 124 that genetically engineering the antibody, such as by humanization, may facilitate the use of the antibodies as neurodiagnostic or therapeutic agents in humans. This was echoed by both Becker and by Ladner, who expressly teach that human monoclonal antibodies and genetically engineered antibodies, such as single chain antibodies, are particularly useful for human therapy due to reduced immunogenicity. As for the functional properties of the claimed antibodies (i.e., inhibition of β-amyloid and/or maintenance of β-amyloid solubility), it is noted that the instant specification discloses no more than the combined teachings of the above references.

12. In the response filed September 23, 2009, Applicant argues that the only specific utility taught by Bickel is a diagnostic utility, and thus the antibody must be conjugated to a detectable moiety. Applicants assert that Bickel does not suggest or enable any use for which such a marker would not be necessary.

13. Applicant's arguments have been fully considered but they are not persuasive. While diagnostic use of the AMY-33 antibody is one utility suggested by Bickel, Bickel also suggests that humanized monoclonal antibodies, or antibodies having reduced immunogenicity, could be used therapeutically. Similarly, Becker teaches therapeutic use of less immunogenic molecules, such as anti-Aβ human monoclonal antibodies and

single chain antibodies, and Ladner extols the benefits of using single-chain antibodies for therapeutic purposes as noted above. In fact, Ladner teaches that single chain antibodies may be used for any purpose envisioned by antibodies, and that the single chain antibody may also be used by itself (i.e., unconjugated to a detectable moiety) in therapeutic uses and compositions. Therapeutic use of such antibodies would not require conjugation to a detectable moiety. Therefore, the combined teachings of the above references render obvious the present invention of claims 177, 210-213, and 215-217.

14. Claims 177, 210-213, 215-217, 219-223 and 225-227 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al. (*J Neuropathol Exp Neurol*. 1994 Jul; 53(4):377-383), as evidenced by Hanan and Solomon (*Amyloid: Int J Exp Clin Invest*. 1996; 3:130-133; of record) and Bacskai et al. (*Nat Med*. 2001; 7(3): 369-372; of record), in view of EP 0613 007 A2 to Becker et al. (published 08/31/1994; of record).

Claims 210, 215 and dependant claims thereof recite a pharmaceutical composition comprising a genetically-engineered antibody, or fragment thereof, that inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and claims 219, 225 and dependent claims thereof recite a pharmaceutical composition comprising a genetically-engineered antibody, or fragment thereof, that disaggregates an aggregate of β-amyloid, wherein the antibody is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen or one that recognizes and epitope within residues

1-28 of β-amyloid, and wherein said antibody or fragment is not conjugated with a detectable moiety. Claims 212, 222 and dependent claims thereof recite a pharmaceutical composition comprising a human monoclonal antibody that inhibits aggregation of human β-amyloid or maintains the solubility of soluble human β-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a human monoclonal antibody that disaggregates an aggregate of β-amyloid, wherein said antibody is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen.

Walker et al. teach the ability of the monoclonal antibody 10D5, and Fab fragments thereof, to label β-amyloid plaques in the brain tissue of aged monkeys. 10D5 antibody or Fab fragments (neither of which were conjugated to a detectable moiety) were administered to the animals and binding of 10D5 was assessed in brain tissue samples 24 hours later (see Injection of Antibody and Immunohistochemistry on p. 378). Walker teaches that the 10D5 antibody can selectively bind to cerebral Aβ. Walker therefore suggests that antibodies such as 10D5 may be employed to deliver therapeutic agents directly to Aβ in the brain, such as for the treatment of β-amyloidoses or Alzheimer's (see p. 381 2nd paragraph, and p. 382, last paragraph). However, Walker does caution that a leukocytic reaction in response to administration of the antibody is of concern for clinical application (p. 382, last paragraph).

As evidenced by Hanan and Solomon, the 10D5 antibody was raised against the peptide consisting of Aβ 1-28 (see p. 131, under "Antibodies") and recognizes an epitope within Aβ 1-28 (see Abstract). In fact, Walker teaches that 10D5 recognizes an

epitope within Aβ 1-16 (see p. 377, 2nd column, 3rd paragraph). Hanan and Solomon evidence that 10D5 is more effective than AMY33 in inhibiting the aggregation of β-amyloid (see p. 132 and Figure 1). Additionally, Bacskai et al. demonstrate that *in vivo* administration of the 10D5 antibody, even for diagnostic purposes such as *in vivo* imaging, results in reduction of brain amyloid deposits in aged PDAPP transgenic mice (an animal model of Alzheimer's disease). See, for example, Figures 2 and 5 and p. 371, 1st paragraph. Thus, Bacskai evidences that the 10D5 antibody is capable of disaggregating an aggregate of β-amyloid. Thus, as evidenced by both Hanan and Solomon and by Bacskai et al., the 10D5 antibody inherently possesses the ability to inhibit soluble β-amyloid aggregation and disaggregate aggregated β-amyloid, both *in vitro* and *in vivo*. A chemical composition and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), as are their processes and yields (*In re Von Schickh*, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)). Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

The difference, therefore, between the prior art teachings of Walker and the instant invention is that Walker does not teach that the antibody is a genetically-engineered antibody such as a single chain antibody.

Becker et al. disclose pharmaceutical formulations comprising a pharmaceutically acceptable carrier and an anti-β-amyloid antibody (see column 8, lines 19-26 and 31-42), such as for use in the diagnosis and treatment of Alzheimer's disease (column 7,

lines 39-52 and column 8, lines16-18). Monoclonal antibodies derived from various species, including mice and humans, are disclosed at column 6, lines 10-19. Thus, Becker teaches the use of anti-β-amyloid human monoclonal antibodies. Becker discloses that the greatest deterrence to the administration to humans of antibodies produced in non-human sources is the risk of hyperimmunogenicity due to the presence of constant regions from the species in which these antibodies are produced. Therefore, genetically engineering the antibodies to retain epitope specificity but reduce immunogenicity is desirable (column 6 lines 31-40). Further, Becker teaches single chain antibodies as another genetically engineered antibody for retaining the binding characteristics of the parental antibody while affording a less immunogenic format (column 7, lines 11-25). Thus, the artisan of ordinary skill in the art would have recognized that such engineered antibodies with reduced immunogenicity would address Walker's concerns about the potential for leukocytic reactions occurring with the clinical use of non-human monoclonal antibodies in humans.

It would have been obvious to one of skill in the art at the time the invention was filed to genetically engineer the 10D5 monoclonal antibody to create a less immunogenic antibody molecule, such as a single chain antibody, for use in therapeutic applications as taught by both Walker et al. and Becker et al. Similarly, it would have been obvious to make a human monoclonal anti-Aβ antibody, as taught by Becker, obtainable using a peptide consisting of residues 1-28 of Aβ because this was the immunogen used to produce the 10D5 antibody, and Walker demonstrates that this antibody binds specifically to brain amyloid deposits, thus evidencing the usefulness of

antibodies obtained with this immunogen. Human monoclonal antibodies would also be less immunogenic when administered to humans, and thus would be advantageous for clinical applications. The skilled artisan would be motivated to make such changes because Walker teaches that the anti-β-amyloid 10D5 antibody is highly useful for providing a means to deliver therapeutic agents to cerebral β-amyloid deposits, but notes that the mouse monoclonal antibody may have immunogenicity issues when used in other species, such as humans. Such antibodies for clinical therapeutic use would not require conjugation to a detectable moiety. Becker teaches that immunogenicity of non-human anti-Aβ antibodies can be reduced whilst still retaining the epitope specificity of the parental antibody by antibody engineering techniques, such as by engineering single chain antibodies from the parental monoclonal antibody or by the use of human monoclonal antibodies. Because such antibody engineering techniques were well-known and established in the art at the time of filing, the artisan would have had a reasonable expectation that the production and use of such engineered antibodies for use in clinical applications in humans would be successful. As noted and evidenced above, the 10D5 antibody taught by Walker inherently possess the capacity to inhibit of β-amyloid aggregation and/or disaggregate aggregated β-amyloid as instantly recited in the claims, and would still be expected to possess such characteristics upon humanization or genetic engineering to produce a single chain antibody. Therefore, the combined teachings of the above references render obvious the presently recited invention of claims 177, 210-213, 215-217, 219-223 and 225-227.

Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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